Electrophysiological Mapping of Embryonic Mouse Hearts: Mechanisms for Developmental Pacemaker Switch and Internodal Conduction Pathway.

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Funding Grants: Development of Neuro-Coupled Human Embryonic Stem Cell-Derived Cardiac Pacemaker Cells., Endothelial cells and ion channel maturation of human stem cell-derived cardiomyocytes

Public Summary:
Using human embryonic stem cell-derived cardiomyocytes (hESC-CMs) and beating embryoid bodies (EBs), we previously showed that intracellular Ca2+ -handling proteins developed early and contributed to dominant automaticity throughout hESC-CM differentiation. Sarcolemmal ion channels evolved later upon further differentiation within EBs and played an increasing role in controlling automaticity and electrophysiological (EP) properties of hESC-CMs. Here, we verify our findings with mouse embryonic embryonic heart preparations at the organ level. We find that dominant pacemaking activity originated from the left inflow tract region at embryonic ages 8.5 days (E8.5), but switched to the right sinus node by E12.5. Additionally, we show that intracellular calcium-mediated automaticity develops early and is the major mechanism of pulse generation in the left inflow tract of E8.5 hearts. Later in development at E12.5, sarcolemmal ion channels develop in the sinus node at a time when pacemaker channels are down-regulated in the left inflow tract, leading to a switch in the dominant pacemaker location. Thus, we demonstrate that differential mechanistic development of automaticity between the left and right inflow tract regions confers the pacemaker location switch. Moreover, we find that a sodium channel independent sinus node- atrioventricular node (internodal) pathway mediates internodal conduction in E12.5 hearts.

Scientific Abstract:
Electrical Mapping of Embryonic Mouse Hearts. Introduction: Understanding sinoatrial node (SAN) development could help in developing therapies for SAN dysfunction. However, electrophysiological investigation of SAN development remains difficult because mutant mice with SAN dysfunctions are frequently embryonically lethal. Most research on SAN development is therefore limited to immunocytochemical observations without comparable functional studies. Methods and Results: We applied a multielectrode array (MEA) recording system to study SAN development in mouse hearts acutely isolated at embryonic ages (E) 8.5-12.5 days. Physiological heart rates were routinely restored, enabling accurate functional assessment of SAN development. We found that dominant pacemaking activity originated from the left inflow tract (LIFT) region at E8.5, but switched to the right SAN by E12.5. Combining MEA recordings and pharmacological agents, we show that intracellular calcium (Ca(2+))-mediated automaticity develops early and is the major mechanism of pulse generation in the LIFT of E8.5 hearts. Later in development at E12.5, sarcolemmal ion channels develop in the SAN at a time when pacemaker channels are down-regulated in the LIFT, leading to a switch in the dominant pacemaker location. Additionally, low micromolar concentrations of tetrodotoxin (TTX), a sodium channel blocker, minimally affect pacemaker rhythm at E8.5-E12.5, but suppress atrial activation and reveal a TTX-resistant SAN-atrioventricular node (internodal) pathway that mediates internodal conduction in E12.5 hearts. Conclusions : Using a physiological mapping method, we demonstrate that differential mechanistic development of automaticity between the left and right inflow tract regions confers the pacemaker location switch. Moreover, a TTX-resistant pathway mediates preferential internodal conduction in E12.5 mouse hearts. (J Cardiovasc Electrophysiol, Vol. pp. 1-10).

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